I040
INDIVIDUAL CHARACTERISTICS INFLUENCE BLOOD PRESSURE RESPONSE TO ANTIHYPERTENSIVE DRUGS

Y. WU [1], T. BEJAN-ANGOULVANT [1], R. BOUSSAGEON [2], F. GUEYFFIER [1]
[1] *Hospices Civils de Lyon; CIC201-Inserm; UMR5558-CNRS, Lyon, France*
[2] *Département Médecine générale, UCBL, Lyon, France*

Introduction — Antihypertensive treatment decreases cardiovascular risk mostly through blood pressure reduction. The current prescription strategy for the choice of drug between the five main antihypertensive classes relies upon intuitive or random choice by the physician. The objective of our analysis was to explore whether systolic blood pressure (SBP) reduction with diuretics, beta-blockers (BB), and calcium channel blockers (CCB), was related to the baseline individual characteristics, and quantify these potential associations.

Methods — We used data from 32767 patients recruited in five randomized placebo-controlled clinical trials in the INDANA database. The main outcome was the SBP fall (DSBP) between randomization and first follow-up visit. Multiple linear regression analyses were used to evaluate the relationship between DSBP, treatment, baseline characteristics of patients, and interactions between these covariates and treatment. Significance level of $p<0.10$ was used for all analyses.

Results — The average DSBP were 10, 8, 5 mmHg with diuretics, BB, and CCB classes respectively. Baseline SBP was significantly correlated to DSBP whatever the drug class. Age and baseline diastolic blood pressure were significantly correlated to DSBP for diuretics and BB, but not for CCB. With BB, height was positively correlated to DSBP, while smoking status was negatively correlated to DSBP.

Conclusion — Some individual characteristics explain a significant part of blood pressure reduction with drugs. These results will be integrated in algorithms to predict clinical benefit from these drugs.

I041
IMPACT DE LA TRANSPLANTATION RÉNALE SUR LA VÉLOCITÉ DE L'ONDE DE POULS

C. BACHELET-ROUSSEAU [1], A. KEARNEY-SCHWARTZ [2], L. FRIMAT [1], M. KESSLER [1], A. BENETOS [2]
[1] *Département de néphrologie, Nancy, France*
[2] *CIC-EC, Nancy, France*

La maladie vasculaire du patient insuffisant rénal terminal est caractérisée par la coexistence de lésions d'athérosclérose et d'artériosclérose, cette dernière conduisant à une rigidité artérielle (RA). On sait que RA est un facteur indépendant de mortalité cardio-vasculaire chez le patient dialysé. Peu de données sont disponibles sur son évolution après transplantation rénale.

Objectifs — étudier l'évolution de la RA après transplantation rénale, dans une population de patients en IRCt, et la comparer à celle de patients restant en dialyse.

Matériel et Méthodes — 100 patients en IRCt candidats à une première transplantation ont été inclus, âge compris entre 35 et 65 ans. Une première mesure de RA a été effectuée lors de l'inclusion, la deuxième 1 an après.

Résultats — l'âge moyen : 54 ± 7 ans, 35 patients ont été transplantés après un an de suivi. La VOP moyenne tendait à diminuer chez les transplantés entre les 2 visites (10.18 ± 3.41 m/s à V1, 9.90 ± 2.61 m/s à V2) sans différence significative, alors qu'elle restait stable chez les dialysés (10.62 ± 3.76 m/s à V1, 10.50 ± 3.61 m/s à V2). On constatait chez les transplantés une diminution significative des PAD et PAM périphériques (81 ± 13 mmHg à V1 vs 76 ± 10 mmHg à V2, 99 ± 14 mmHg à V1 vs 94 ± 10 mmHg à V2) et centrales (80 ± 14 mmHg à V1 vs 74 ± 10 mmHg à V2, 99 ± 14 mmHg à V1 vs 94 ± 09 mmHg à V2). La VOP post-greffe était significativement corrélée à la diminution de la PAM, n'était pas corrélée au degré de filtration glomérulaire, au temps d'exposition après transplantation ou à l'âge du donneur. La diminution de la VOP était significativement corrélée à la diminution de la PAM.

Conclusion — dans cette étude, la diminution de la VOP corrélée à la diminution de la PAM suggèrerait un effet indirect possible de la transplantation sur l'évolution de la VOP. L'amélioration du pronostic cardio-vasculaire pourrait être expliquée chez les transplantés par la diminution des PAD et PAM périphériques et centrales après greffe.

Vendredi 3 avril 2009, de 11 h 00 à 12 h 30
J — SIGNALISATION CARDIAQUE ET VASCULAIRE

J001
COMPARISON OF LENGTH-DEPENDENT CA^{2+} ACTIVATION OF CARDIAC MYOFILAMENTS BETWEEN THE RAT AND THE RAINBOW TROUT

S. PATRICK [1], H. SHIELS [1], O. CAZORLA [2]
[1] *University of Manchester, Manchester, United Kingdom*
[2] *Inserm U637, Montpellier, France*

Most fish regulate cardiac output via changes in stroke volume whereas most mammals regulate cardiac output via changes in heart rate. We hypothesized that this change in mechanism of regulation would coincide with a change in the myocardial response to stretch. This possibility was tested in permeabilized cardiomyocytes prepared from rat and rainbow trout ventricles, where both sarcomere length (SL) and degree of Ca2+ activation could be controlled. Myofilament Ca2+ sensitivity activation was higher in trout than in rat at each SL tested (2.0, 2.3, 2.5 and 2.7 ìm). We also found that permeabilized trout myocytes produce greater passive tension at any given SL than rat. This was surprising as the trout heart is known to be more compliant. Interestingly, addition of phosphatase inhibitors in the permeabilizing solution reduced passive tension in the trout cells suggesting that phosphorylation of titin may be important in determining passive tension in particular in trout heart. In conclusion contractile properties in trout seem highly sensitive to the length-dependent modulation.

J002
THE CAMP BINDING PROTEIN EPAC REGULATES CARDIAC MYOFILAMENT FUNCTION

O. CAZORLA [1], A. LUCAS [2], A. LACAMPAGNE [1], F. LEZOUALCH [2]
[1] *Inserm U637, Montpellier, France*
[2] *Inserm U769, Chatenay-Malabry, France*

In the heart, cAMP is a key regulator of excitation—contraction coupling and its biological effects are mainly associated with the activity of protein kinase A (PKA). The aim of this study was to

investigate the contribution of the cAMP-binding protein Epac (Exchange protein directly activated by cAMP) in the regulation of the contractile properties of rat ventricular cardiac myocytes. We report that both PKA and Epac increased cardiac sarcomere contraction but through opposite mechanisms. Differently from PKA, selective Epac activation by the cAMP analog 8-pCPT reduced Ca2+ transient amplitude and increased cell shortening in intact cardiomyocytes as well as myofilament Ca2+ sensitivity in permeabilized cardiomyocytes. Moreover, ventricular myocytes, which were infected in vivo with a constitutively active form of Epac, showed enhanced myofilament Ca2+ sensitivity compared to control cells infected with GFP alone. At the molecular level, Epac increased phosphorylation of two key sarcomeric proteins, cardiac Troponin I (cTnI) and cardiac Myosin Binding Protein-C (cMyBP-C). The effects of Epac activation on myofilament Ca2+ sensitivity and on cTnI and cMyBP-C phosphorylation were independent of PKA, and were blocked by protein kinase C (PKC) and Ca2+ calmodulin kinase II (CaMKII) inhibitors. Altogether these findings identify Epac as a new regulator of myofilament function.

J003

HEMIN PREVENTS IN STENT RESTENOSIS IN RAT AND RABBIT MODELS: HEME OXYGENASE-1 AS A NEW THERAPEUTIC TARGET TO PREVENT RESTENOSIS

B. MAUREL [1], R. UZBEKOV [2], R. MOTTERLINI [3], P. LERMUSIAUX [1], J.-M. HYVELIN [1]

[1] Laboratoire de Physiopathologie de la Paroi Artérielle, EA3852, Faculté de Médecine, Université François Rabelais, Tours, France
[2] Service de Biologie Cellulaire et Microscopie Electronique, Hôpital Bretonneau, CHRU de Tours, Tours, France
[3] Department of Drug Discovery and Development, Italina Institute of Technology, Genova, Italy

Recent reviews have concluded that although drug eluting stent (DES) are efficient in reducing in stent restenosis, their use does not have a significant effect on overall long-term survival as compared with bare metal stent. DES is associated with delayed vascular wall healing and endothelial function restoration, which mandates longer-term dual antiplatelet therapy. Recent studies demonstrated that the microsatellite polymorphism in the promoter of heme oxygenase-1 (HO-1) gene is related to angiographic restenosis. HO-1 is a rate-limiting enzyme in heme degradation; leading to the generation of free iron, biliverdin, and carbon monoxide (CO). HO-1 is recognized to offer protection in many cardiovascular disorders. We aim to assess the potential protective effect of hemin, a potent HO-1 inducer, in the development of ISR in both rat and hypercholesterolemic rabbit.

In a rat model of aorta stenting and rabbit iliac stenting, chronic treatment with hemin (50 mg/kg/48h/ip) reduced neointima growth (-30% and -50% in hemin-treated rats and rabbits respectively), and most importantly stent struts remained covered, contrarily to the use of sirolimus eluting stent. Analysis of the cells facing the arterial lumen (electron microscopy) revealed an ultra-structure similar to endothelial cells and the expression of CD31 (immunogold labeling). Endothelial coverage was similar in hemin-treated rats and greater in hemin-treated rabbits when compared to their control groups. Analysis of protein expression, in rats, revealed that hemin, limited the early inflammatory, apoptotic and proliferative cellular events common to ISR. More particularly, hemin treatment was associated with a decrease activity of key regulators of smooth muscle cell migration and proliferation, p42/44, RhoA and an increase of the expression of both cyclin dependent kinase inhibitors, p21 andp27kip1. This beneficial effect of hemin was abolished in presence of SnPP, an inhibitor of HO-1. Finally, CORM-3, a specific carbon monoxide donor, limited ISR.

In conclusion, hemin reduced neointima growth without compromising re-endothelialization of the stented arteries. HO-1 plays important role in limiting neointima growth, at least through the production of CO, and can be regarded as a new therapeutic target to prevent ISR.

J004

DARBEPOETIN-<ALPHA> PROTECTS HEART AGAINST ISCHEMIA-REPERFUSION: ROLE OF BCL-2 FAMILY PROTEINS

D. SCHLECHT-BAUER [1], D. ANTIER [1], M.-C. MACHET [1], J.-M. HYVELIN [1]

[1] Laboratoire de Physiopathologie de la Paroi Artérielle, EA3852, Faculté de Médecine, Université François Rabelais, Tours, France

Heart can usually survive a short period of ischemia, but when this period is too long, damages of the cardiac tissue became irreversible and are possibly exacerbated by blood reperfusion. Loss of cardiac myocytes via apoptosis is believed to contribute to the continuous decline of ventricular function described in heart failure. Limiting theses deleterious responses is of major importance in cardiac surgery and for the treatment of coronary thrombosis. The purpose of this study was to assess the short and long term cardioprotective effects of the long lasting effect erythropoietin analogue darbepoetin-α (DA) in a myocardial ischemia-reperfusion model in rat and; to investigate the signaling pathway through which DA potentially limits apoptosis of cardiomyocytes.

Rat were subjected to 40 min left coronary artery ligation followed by 3h, 72 h or 4 weeks reperfusion and they received either DA (3 or 30 µg/kg) or vehicle i.v. prior ischemia. Left ventricle (LV) function was assessed by echocardiography prior surgery and after reperfusion. Hearts were collected for histological analysis, protein analysis and reactive oxygen species (ROS) production.

In DA3 and DA30 72hrs groups, both LV shortening fraction and LV ejection fraction were higher vs. control ($P<0.05$), matching with histological analysis revealing a relative LV infarct size 72h post ischemia of 40 ± 5% in control vs. 27 ± 3 and 17 ± 2% in DA3 and DA30, respectively. DA treatment lowered ROS production, the activity of caspase 3 in 3h and 72h reperfusion groups, and activated the JAK2/AkT signaling pathway and then increased both phosphorylated Bad and GSk3β proteins. This was consistent with the decrease of Bad-Bcl-Xl in DA30 group, suggesting an increased level of Bcl-Xl protein. Similar results were obtained in DA-treated rats reperfused 4 weeks; in which cardiac fibrosis was significantly lower than that in control group.

DA pre-treatment limited in a dose dependent manner the early and late I/R-induced heart injury in rat. Anti-apoptotic effects mediated through the activation the survival kinase Akt that regulates the Bcl-2 family proteins and activates GSK-3β is central in the DA cardioprotective mechanism.